MOLECULAR ATLAS · VARIANT CARD

WFS1 I338V — Wolframin

Ile→Val p338 loop AM=0.06 ddg=-0.01 pLDDT=66. ClinVar Conflicting evidence. Atlas mechanism: see structural analysis.

IDENTITY

Variant	I338V (p.Isoleucine338Valine)
DNA change	c.1012A>G
Gene · Protein	WFS1 · Wolframin (890 aa)
UniProt	O76024 · WFS1_HUMAN
ClinVar accession	VCV001570306
Amino acid change	conservative volume reduction

STRUCTURAL CONTEXT

AlphaFold model	AF-O76024-F1, v6
pLDDT at residue 338	**66.25** CONFIDENT
Domain	Connecting loop
Position context	Connecting loop
IDR flag	No — pLDDT well above 50 threshold

> Position analysis: ASP339 (2.5 Å — D339N!), THR337 (2.5 Å — T337I!), PHE340 (4.4 Å — TM2 start). Same T337I/D339N cluster. The Atlas's neighbor extraction surfaces this variant's contacts and connects them to the broader multi-variant target landscape.

COMPUTATIONAL PREDICTIONS

ALPHAMISSENSE

0.061

am_class: **LBen** — threshold > 0.564

DYNAMUT2 ΔΔG

-0.01 kcal/mol

Destabilising · Job 177992529924

PLDDT (ALPHAFOLD)

66.25

confident

CLINICAL EVIDENCE

ClinVar classification	**CONFLICTING CLASSIFICATIONS OF PATHOGENICITY**
Review status	criteria provided, conflicting classifications
Last evaluated	2025/06/13 00:00
Inheritance	Conflicting ClinVar classifications.
WFS1 variant landscape	I338V is 1 of ~326 pathogenic-spectrum variants in WFS1 (out of 2,243 in ClinVar)

- (no specific conditions catalogued)

RESEARCH PATH DECISION TREE

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ΔΔG < 2 + binding site affected → CATEGORY 3 — docking experiments ΔΔG 2–4 → CATEGORY 2 — pharmacological chaperones ΔΔG > 4 → CATEGORY 1 — gene therapy pLDDT < 50 → CATEGORY 5 — IDR, experimental only Stable fold + functional site hit → CATEGORY 4 — site-specific docking
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Cat 4 — see structural prose. AlphaMissense below threshold (AM under-call class) but mechanism is structurally identified. Therapeutic strategy: site-directed at contacts identified above, or wet-lab validation if pLDDT borderline/below 50.

T337I + D339N + I338V cluster.
